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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/764,921	01/26/2004	David B. Volkin	19907YIACB	9882

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EXAMINER	
WEHBE, ANNE MARIE SABRINA	
ART UNIT	**PAPER NUMBER**
1633	

DATE MAILED: 11/15/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/764,921	VOLKIN ET AL.	
	Examiner	Art Unit	
	Anne Marie S. Wehbe	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 October 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-40* is/are pending in the application.

4a) Of the above claim(s) *27-40* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response to the restriction/election requirement received on 10/6/06 has been entered. Applicant's election of Group I and the species HIV without traverse is acknowledged. Claims 1-40 are pending in the instant application. Upon further consideration, however, the examiner has withdrawn the election of species requirement for "antigens". The restriction requirement is maintained as the applicant has elected Group I without traverse. Claims 27-40 are therefore withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Claims 1-26 are currently under examination in the instant application. An action on the merits follows.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-26 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of inducing an immune response in a host comprising the intramuscular administration of a pharmaceutical composition comprising a plasmid DNA encoding a viral antigen and an aluminum phosphate based adjuvant wherein the expression of said viral antigen in said host results in the generation of an antigen-specific immune response,

does not reasonably provide enablement for methods of inducing a prophylactic or therapeutic immune response against any disease or disorder comprising the administration of a composition comprising any vector encoding any antigen and an aluminum phosphate based adjuvant using any route of administration. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. Please note that while claims 1-14 and 27-31 recite pharmaceutical formulations, these claims are properly included in this rejection based on the intended use for these formulations in vivo for treating or preventing disease as recited in the claims and disclosed in the specification.

The specification discloses that polynucleotides encoding an antigen can be combined with a mineral based, negatively charged adjuvant, such as an aluminum phosphate based adjuvant, and administered to a mammal resulting in the generation of therapeutic or prophylactic immune responses against diseases or disorders associated with the expressed antigen. Diseases and disorders identified by the specification include cancer, allergy, autoimmune disease, and both bacterial and viral infections. The specification further discloses that the polynucleotides encoding the antigen can include both plasmid vectors and viral vectors such as adenoviruses and retroviruses. The specification's working examples are limited to the demonstration that the intramuscular injection of various plasmid DNA vectors encoding a viral antigen complexed with aluminum phosphate or calcium phosphate into mice can result in the generation of both humoral and cellular immune responses capable of protecting against infection against viruses such as Influenza or HBV. The specification does not provide any concrete data concerning the use of vectors other than plasmid DNA vectors, the use of routes of

administration other than intramuscular injection, or the generation of immune responses against antigens other than viral antigens.

The specification does not provide sufficient guidance for generating any kind of immune response, including prophylactic or therapeutic immune responses, using any antigen, any vector, and any dosage and route of administration. At the time of filing the prior art identifies several factors which significantly affect the generation of immune responses to an antigen which include, genetics, dose or concentration of antigen, and route of antigen administration (Abbas et al. (1996) Nature, Vol. 383, 787-793, and Golding et al. (1994) Am. J. Trop. Med. Hyg., Vol. 50 (4), 33-40). The prior art teaches that the concentration of antigen significantly affects the development of cellular (Th1) versus humoral(Th2) immune responses such that low antigen concentrations preferentially induce Th1 type responses and high concentrations of antigen induce Th2 type responses (Abbas et al., *supra*). The antigens themselves have also been reported to affect the type of immune response generated. For example intracellular microorganisms such as *Salmonella, Leishmania, Malaria* and *Listeria* typically induce Th1 type responses, whereas schistosomiasis and *Nippostongylus* typically induce Th2 type responses. A further complicating factor is the genetic background of the infected mammal. The prior art contains numerous reports which demonstrate the Balb/C mice versus C57Bl/6 mice develop different responses to various pathogens. The nature and route of administration of the antigen is also of concern to the generation of a particular T helper phenotype. Golding et al. teaches that intravenous or intraperitoneal immunization leads to preferential induction of Th1 cells whereas subcutaneous or intramuscular immunization leads to Th2 cells which may be attributable to the participation of various antigen-presenting cells (Golding et al., *supra*). Thus, the art at the time

of filing clearly teaches that a significant number of variables affect the generation of specific immune responses which render the generation of a particular type of immune response in any mammal unpredictable for any given antigen.

Furthermore, the strength and nature of the immune response generated by a particular antigen was known at the time of filing to be critical to its ability to successfully protect against infection. A weak immune response, or an immune response that only generates antibodies and no CTL may be insufficient to protect against many pathogens. In the case of pseudorabies virus, Monteil et al. discloses that the immunization of naive one-day-old piglets with a plasmid DNA encoding the gene for the gD glycoprotein induces antibodies which do not protect the piglets from PRV challenge (Monteil et al. (1996) Veterinary Research, Vol. 27 (4-5), page 443, abstract). Ertl and Zhiang concur, stating that, " although any antigens can be delivered by genetic immunization, some proteins upon expression by plasmid vectors remain immunologically silent. The principles that govern success versus failure of genetic immunization with regard to each individual protein remain to be elucidated" (Ertl et al. (1996), Viral Immunology, Vol. 9 (1), page 2, lines 32-35).Yasutomi et al. further teaches that immunization of rhesus monkeys with a live viral vector which encodes the SIV gag protein generate a non-protective CTL response, but fails to generate a humoral immune response despite the presence of MHC class II and antibody binding epitopes in the gag protein (Yasutomi et al. (1995) J. Virol., Vol. 69 (4), page 2279, abstract). In addition, Yasutomi et al. teaches that while boosting vaccinated animals with a gag peptide/liposome complex significantly increases the anti-gag CTL response, it still did not provide increased protection against SIV challenge (Yasutomi et al., *supra*, abstract). The situation is even more complicated in the case of raising

therapeutic immune responses against tumors. In order for a cytolytic T cell to kill a target tumor cell, the tumor cell must be presenting sufficient amounts of specific peptide/MHC class I complexes on the cell surface. The literature teaches that tumors evade immune response by a variety of mechanisms including loss of antigenic epitopes by either lack of expression or mutations, loss of functional β-$_2$m expression or of particular MHC class I alleles, and down-regulation of putative antigen processing molecules, including TAP and MHC-encoded proteosome components (Restifo et al (1993) J. Immunother., Vol. 14, page 183, col 1, lines 8-14, and page 184, col. 2). In addition, both allergy and autoimmune diseases are caused by inappropriate immune responses to either self or environmental proteins. At the time of filing, the state of the art of treatment for both allergy and autoimmune disease focused on the **inhibition** or **tolerization** of immune responses to allergens and autoantigens. The specification fails to provide any guidance or evidence regarding how the induction of immune responses against an allergen or autoantigen can result in the protection or treatment of these diseases. Therefore, due to the variability in immunogenicity between different proteins based on their structure and cellular location, and the nature of various types of antigens and their associated diseases, the skilled artisan would not have been able to predict whether vaccination using the instant methodology with any disease associated antigen would result in a protective or therapeutic immune response.

Further, at the time of filing, in vivo gene therapy utilizing the direct administration of recombinant nucleic acids, whether in the form of vaccinia virus, adenoviruses, or plasmid DNA/liposome complexes, was considered to be highly unpredictable. Verma et al. states that, "[t]he Achilles heel of gene therapy is gene delivery..", and that, "most of the approaches suffer

from poor efficiency of delivery and transient expression of the gene" (Verma et al. (1997) Science, Vol. 389, page 239, column 3, paragraph 2). Marshall concurs, stating that, " difficulties in getting genes transferred efficiently to target cells- and getting them expressed- remain a nagging problem for the entire field", and that, "many problems must be solved before gene therapy will be useful for more than the rare application" (Marshall (1995) Science, Vol. 269, page 1054, column 3, paragraph 2, and page 1055, column 1). Orkin et al. further states in a report to the NIH that, " .. none of the available vector systems is entirely satisfactory, and many of the perceived advantages of vector systems have not been experimentally validated", and that," [w]hile the expectations and the promise of gene therapy are great, clinical efficacy has not been definitively demonstrated at this time in any gene therapy protocol" (Orkin et al. (1995) "Report and recommendations of the panel to assess the NIH investment in research on gene therapy", page 1, paragraph 3, and page 8, paragraph 2). Thus, in view of the unpredictable state of the art of in vivo vector administration at the time of filing, the variability in immunogenicity between different proteins based on their structure and cellular location, the nature of various types of antigens and their associated diseases, the lack of guidance provided by the specification for administering any vector encoding any antigen using any route of administration, the limitation of applicant's working examples to the intramuscular injection of plasmid DNA vectors encoding viral antigens, and the breadth of the claims, it would have required undue experimentation for the skilled artisan to practice the full scope of applicant's invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 3-8, 11-12, and 15-26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 3 is indefinite because the phrase "does not substantially bind to nucleic acid molecules" is unclear as to its metes and bounds. The term "substantially" is relative and as such it is unclear what is encompassed within this term such that one of skill in the art could determine what "substantially binds" means.

Claims 5 and 6 contain the trademark/trade name Adju-Phos. Where a trademark or trade name is used in a claim as a limitation to identify or describe a particular material or product, the claims does not comply with the requirements of 35 U.S.C. 112, second paragraph. See *Ex parte Simpson*, 218 USPQ 1020 (Bd. App. 1982). The claim's scope is uncertain since the trademark or trade name cannot be used properly to identify and particular material or product. A trademark or trade name is used to identify a source of goods, and not the goods themselves. Thus, a trademark or trade name does not identify or describe the goods associated with the trademark or trade name. In the present case, the trademark/trade name is used to identify/describe an aluminum phosphate based solution, and accordingly, the identification/description is indefinite. Since the exact composition of the trademark aluminum phosphate based adjuvant "Adju-Phos" cannot be determined, claims reciting the use of "Adju-Phos" have been interpreted to read on the use of any aluminum phosphate based adjuvant.

Claims 4, 7-8, 11-12, and 15-26 depend on rejected claims 3, 5, or 6 and as such are included in these rejections.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (e) the invention was described in-
> (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effect under this subsection of a national application published under section 122(b) only if the international application designating the United States was published under Article 21(2)(a) of such treaty in the English language; or
> (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that a patent shall not be deemed filed in the United States for the purposes of this subsection based on the filing of an international application filed under the treaty defined in section 351(a).

Claims 1-6, 15-27, 32, 35, and 38 are rejected under 35 U.S.C. 102(e) as being anticipated by U.S. Patent No. 5,808,024, 9/15/98, hereafter referred to as Sasaki et al. The applicant claims pharmaceutical compositions comprising a polynucleotide vaccine encoding an antigen and a mineral-based, negatively charged adjuvant, which is an aluminum phosphate based adjuvant ,and methods of administering said pharmaceutical composition to a mammal to induce an immune response against said encoded antigen.

Sasaki et al. teaches vaccines against bacterial infections comprising a recombinant vector encoding a moraxella antigen and methods of generating therapeutic immune responses against moraxella comprising administering the vector to a mammal (Sasaki et al, columns 3-4, and columns 27-30, claims 1-13). Sasaki et al. further teaches administering said vaccine vectors in combination with adjuvants such as aluminum phosphate (Sasaki et al., column 3, lines 57-63). In addition, Sasaki et al. teaches that the vaccines may be administered to a mammal either

subcutaneously or intramuscularly (Sasaki et al., column 8, lines 29-31). Thus, by teaching all the elements of the claims, Sasaki et al. anticipates the instant invention.

Claims 1-10, and 15- 26 are rejected under 35 U.S.C. 102(e) as being anticipated by U.S. Patent No. 5,925,362, 7/20/99, hereafter referred to as Spitler et al. The applicant claims pharmaceutical compositions comprising a polynucleotide vaccine encoding an antigen and a mineral-based, negatively charged adjuvant which is an aluminum phosphate based adjuvant, and methods of administering said pharmaceutical composition to a mammal to induce an immune response against said encoded antigen. The applicant further claims said methods wherein the administration is intramuscular.

Spitler et al. teaches method of generating therapeutic anti-tumor immune responses by administering DNA expression system encoding the tumor antigen PSA in combination with the adjuvant alum (Spitler et al., column 9-10, claims 1-8). Alum is well known in the art as a aluminum phosphate based adjuvant. In addition, Spitler et al. teaches the intramuscular administration of the prostate cancer vaccine (Spitler et al., column 8). Thus, by teaching all the elements of the instant invention, Spitler et al. anticipates the invention as claimed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made

> to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Xiang et al. (1994) Virol., Vol. 199, 132-140, in view of U.S. Patent No. 5,925,362, 7/20/99, hereafter referred to as Spitler et al., and U.S. Patent No. 5,808,024, 9/15/98, hereafter referred to as Sasaki et al.. The applicant claims pharmaceutical compositions comprising a polynucleotide vaccine encoding an antigen and a mineral-based, negatively charged adjuvant, which is an aluminum phosphate based adjuvant, and methods of administering said pharmaceutical composition to a mammal to induce an immune response against said encoded antigen. The applicant further claims wherein the antigen is an antigen associated with tumor growth or rabies, wherein the polynucleotide vaccine is a plasmid, and wherein the pharmaceutical composition is administered intramuscularly to a host.

Xiang et al. teaches the intramuscular injection of mice with a plasmid vector encoding the rabies virus G protein under transcriptional control of the SV-40 promoter resulting in the

generation of rabies specific antibodies capable of protecting the vaccinated mice from challenge with live rabies virus (Xiang et al., page 134, column 1, and pages 137-139, Figures 3-7).

Xiang et al. differs from the instant invention by failing to teach the combination of a plasmid vaccine with aluminum phosphate adjuvant. Sasaki et al. supplements Xiang et al. by teaching that the administration of vaccines comprising a vector encoding a pathogenic antigen and adjuvants such as aluminum phosphate can be used to generate therapeutic immune responses in vivo (Sasaki et al, columns 3-4, and columns 27-30, claims 1-13). Spitler et al. further supplements Xiang and Sasaki by teaching methods of generating therapeutic anti-tumor immune responses by administering DNA expression system encoding the tumor antigen PSA in combination with the adjuvant alum (Spitler et al., column 9-10, claims 1-8). Both Sasaki et al. and Spitler et al. provide motivation for combining polynucleotide vaccine with adjuvants such as aluminum phosphate by teaching that adjuvants can enhance immune responses (Sasaki et al., column 3, and Spitler et al., column 7). Thus, based on the motivation to combine aluminum phosphate based adjuvants with polynucleotide vaccines taught by Sasaki et al. and Spitler et al., it would have been *prima facie* obvious to the skilled artisan at the time of filing to include aluminum phosphate or alum with the plasmid encoding the rabies virus G protein taught by Xiang et al. in order to enhance immune responses in vivo. Based on the successful use of the plasmid taught by Xiang et al. to induce anti-rabies immune responses, and the known function of aluminum phosphate adjuvants to enhance immune responses, the skilled artisan would have had a reasonable expectation of success in generating immune responses against a rabies antigen by intramuscular injection of a composition comprising a plasmid encoding a rabies antigen and aluminum phosphate

Further, based on the successful use of intramuscular injection of a plasmid DNA encoding an antigen to generate immune responses in vivo taught by Xiang et al., it would have been *prima facie* obvious to the skilled artisan to use the plasmid vector taught by Xiang et al. in the method of generating immune responses against PSA taught by Spitler et al. with a reasonable expectation of success.

No claims are allowed.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (571) 272-0737. If the examiner is not available, the examiner's supervisor, Dave Nguyen, can be reached at (571) 272-0731. For all official communications, **the new technology center fax number is (571) 273-8300**. Please note that all official communications and responses sent by fax must be directed to the technology center fax number. For informal, non-official communications only, the examiner's direct fax number is (571) 273-0737. For any inquiry of a general nature, please call (571) 272-0547.

The applicant can also consult the USPTO's Patent Application Information Retrieval system (PAIR) on the internet for patent application status and history information, and for electronic images of applications. For questions or problems related to PAIR, please call the USPTO Patent Electronic Business Center (Patent EBC) toll free at 1-866-217-9197. Representatives are available daily from 6am to midnight (EST). When calling please have your

application serial number or patent number available. For all other customer support, please call the USPTO call center (UCC) at 1-800-786-9199.

Dr. A.M.S. Wehbé

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PRIMARY EXAMINER